Risk Factors for the Development of Placebo Adverse Reactions in a Multicenter Clinical Trial

JOSEPH A. TANGREA, RPH, MPH, MARIA ELENA ADRIANZA, BA, AND WILLIAM E. HELSEL, MSc

ABSTRACT *In this report, we examine the potential risk factors for both the incidence and the number of placebo adverse reactions among patients who were enrolled in the placebo control group in a multicenter clinical trial (n = 491). Of the nine baseline covariates analyzed, only clinical center was significantly related to both the presence and the number of adverse reactions. Placebo group patients at clinical centers 5 and 7 were more than twice as likely to experience an adverse reaction than were patients at clinical center 1. This finding, in light of the intensive effort we made to standardize the methods for adverse reaction detection and management, points out the difficulty in controlling for the inherent differences in the characteristics of the patient populations and clinic personnel at the clinical centers in a multicenter trial, and reinforces the need to stratify by clinical center prior to randomization. Ann Epidemiol 1994;4:327–331.*

KEY WORDS: Placebo, risk factors, adverse reactions, clinical trial, multicenter

BACKGROUND AND INTRODUCTION

Inactive preparations, known as placebos (from the Latin "I shall be pleasing"), have been used for centuries by physicians and medical healers as a psychological tool in the therapy of neurotic ailments and psychoses as well as to distinguish the true effects of a drug from mere suggestion. Today, placebos are commonly included as control treatments in clinical trials. Use of a placebo allows the investigator to distinguish real drug effects from non-drug-related effects and from the natural course of the disease under study, thus avoiding bias in estimates of true drug properties (1). Although the usual purpose of including a placebo in a clinical trial is to correct for the effects of a treatment, it may also be used to fulfill the requirements for double-masked design, to achieve a period of "washout" before or between active treatments, or to assess patient compliance during a "run-in" period before the start of a trial.

It is generally accepted that a large component of the placebo response is psychological in nature. Much research has been done to ascertain potential factors that may help distinguish placebo "reactors" from "nonreactors" (2–5). Indeed, several studies have focused on the potential "side effects" of placebos and the predictive value of such determinants as demographic characteristics, preexisting medical conditions, dose, and the clinical milieu in which the placebo was administered (6–13).

In this report, we examine the potential risk factors for placebo-related adverse reactions among patients who were enrolled in the placebo control group in a multicenter clinical trial designed and directed by the National Cancer Institute. This study evaluated the effectiveness of a low-dose regimen of isotretinoin administered over 3 years, in preventing new basal cell carcinomas (BCCs) in patients at high risk for these skin tumors (14). We recently reported on treatment group differences in the incidence of laboratory and clinical adverse effects and the baseline risk factors for developing these (15).

METHODS

The Clinical Trial and Study Population

The Isotretinoin–Basal Cell Carcinoma Prevention Trial (ISO-BCC Study) was a double-blind, randomized, placebo-controlled clinical trial conducted by the Division of Cancer Prevention and Control, National Cancer Institute (16).

Between 1984 and 1987, a total of 981 white men and women, between the ages of 40 and 75 years, were recruited and, after meeting strict eligibility criteria, enrolled at eight clinical centers in the United States (16). Patients were randomly assigned to receive either 10 mg of isotretinoin or a matching placebo (both supplied by Hoffmann LaRoche, Nutley, NJ) daily, for 3 years. To monitor for skin cancer

From the Cancer Prevention Studies Branch, Division of Cancer Prevention and Control, National Cancer Institute, National Institutes of Health, Bethesda (J.A.T.) and Information Management Services, Silver Spring (M.E.A., W.E.H.), MD.

Address reprint requests to: Joseph A. Tangrea, RPh, MPH, Deputy Chief, Cancer Prevention Studies Branch, DCPC, NCI, NIH, EPN, Room 211, 9000 Rockville Pike, Bethesda, MD 20892.

Received August 9, 1993; revised November 16, 1993.

1047-2797/94/$07.00

AEP Vol. 4, No. 4
July 1994: 327–331

and potential adverse effects, patients reported for follow-up clinic visits at 2 weeks, 3 months, 6 months, and every 6 months thereafter for the duration of the 3 years of intervention. Results of the study showed no protective effect of isotretinoin on the occurrence of new BCCs. We found no difference in the 3-year cumulative incidence of BCC or in the annual BCC tumor rate between the isotretinoin and placebo groups (14).

Detection, Classification, and Management of Adverse Effects

For the purpose of this trial, an adverse event was defined as any effect, unpleasant or harmful, a patient might experience on either a temporary or a permanent basis. *All* potential adverse effects, whether in the isotretinoin or placebo group, were systematically elicited, classified, managed, and documented during the course of the trial using a standardized, comprehensive approach, as follows (17).

In order to establish a baseline with which to compare symptoms and laboratory values measured over the course of the trial, we elicited information on symptoms and medical conditions present within the year preceding randomization through a standardized screening process. At the baseline visit, physical complaints or symptoms experienced by the patient within the previous year were elicited through the administration of a standardized questionnaire that focused on various body systems that could be affected by the study medication, isotretinoin (i.e., skin, mucous membranes, muscles, joints, gastrointestinal system, etc.). The questionnaire included a series of questions covering potential symptoms (chapped lips, dry skin, dry eyes, arthralgias, myalgias, nausea, headache, etc.) and an open-ended question to elicit any other complaints from the patient. If a patient reported a symptom as present, its severity was classified as mild, moderate, or severe. To complete the baseline evaluation, the patient underwent a physical examination and selected laboratory tests including a complete blood cell count, blood chemistries, serum lipids, and a urinalysis. The same questionnaire was administered at all subsequent scheduled visits whereas laboratory tests were repeated at 2 weeks, 3 months, 12 months, and yearly through the end of the intervention phase (36 months).

New, recurrent, or worsening symptoms or abnormal laboratory values detected at follow-up visits during the 3-year treatment period were classified in terms of their severity (as mild, moderate, or severe) and association to the study medication (possibly related, remotely related, or not related) according to strict criteria (17). All adverse events, together with their clinical course from initial detection to resolution, were recorded on appropriate data collection forms.

To ensure standardization in the detection, classification, documentation, and management of adverse reactions, clinical center study coordinators (usually nurses or physician assistants) were centrally trained prior to implementation of the trial. In addition, over the course of the trial, both investigators and study coordinators attended periodic group meetings that included additional training sessions, case reviews, and discussion of problems related to the classification or management of adverse events. Throughout the intervention period, the Data Coordinating Center also made weekly telephone calls to each clinical center coordinator to track adverse events as they occurred and provide practical reinforcement of the standard methodology.

Data Analysis and Statistical Methods

In this analysis, we examined both the presence and the average number of adverse reactions in patients assigned to the placebo control group in the trial (n = 491). All placebo adverse effects classified as "not related" or "remotely related" to the study medication were excluded from the analysis. Our primary interest was to examine factors that could influence the reporting of adverse reactions that required the patients' subjective response as elicited by our standardized adverse reaction detection and reporting system. In addition, less than 2% of patients in the placebo group experienced laboratory adverse effects (15). Therefore, for the purpose of this analysis, only nonlaboratory or "clinical" adverse reactions (i.e., mucocutaneous reactions, arthralgias, and myalgias) and other subjective manifestations such as headache and nausea were included. Within the placebo control group, 35% of patients experienced mucocutaneous adverse effects, 8% developed arthralgias or myalgias, and 6% experienced miscellaneous symptoms including headache, nausea, abdominal cramps, blurred vision, dizziness, depression, constipation, and diarrhea (15).

We used unconditional logistic regression analysis (18) to examine the relationship between baseline covariates and the development of an adverse reaction. Patients with data missing from any of the covariates listed were excluded from the analysis. Factors simultaneously evaluated included age, sex, educational status, marital status (to explore demographic and constitutional factors), clinical center (to examine geographic or center-specific differences), smoking status (to examine a significant life-style factor), very fair skin type, and the number of BCCs occurring in the 5 years prior to study entry (to explore factors that influence the development of subsequent BCC). Very fair skin was defined by Fitzpatrick skin type I (always burns easily, never tans) (19). Odds ratios and respective 95% confidence limits were calculated for individual covariates.

Since patients could develop more than one adverse reaction over the 36-month follow-up, we used a log-linear model (18) to examine whether the number of adverse reactions developed over the course of the trial was predicted by any of the risk factors listed above. Once again, patients with data missing for any of the covariates were excluded from the analysis. Since length of follow-up time can influence the number of reactions elicited, we further limited patients in this analysis set to those with a full 36-months of follow-up. Results are presented for each risk factor as a count ratio, defined as the ratio of the average number of adverse reactions over 36 months of intervention for the covariate to the average number of adverse reactions over 36 months of intervention in the reference group, adjusted for all other covariates in the model. Individual risk factor count ratios and their 95% confidence intervals (CIs) were calculated.

RESULTS

Baseline Characteristics

Table 1 presents the baseline characteristics of this patient population. The mean and median ages of the population were 61.5 and 63 years, respectively. This population was predominantly male (79%), married (88%), and college-educated (61%) and had smoked sometime in life (71%).

TABLE 1. Baseline characteristics of study population (n = 480)

Baseline covariate	No. (%)
Age	
< 63 y	235 (49)
⩾ 63 y	245 (51)
Gender	
Male	381 (79)
Female	99 (21)
Education	
⩽ High school	187 (39)
College or greater	293 (61)
Marital status	
Single	14 (3)
Married	420 (88)
Widowed	21 (4)
Divorced/separated	25 (5)
Clinical center	
1	83 (17)
2	51 (11)
3	68 (14)
4	65 (13)
5	44 (9)
6	62 (13)
7	70 (15)
8	37 (7)
Smoking status	
Never smoked	138 (29)
Ever smoked	342 (71)
Skin type	
Very fair skin	103 (21)
Moderate to dark skin	377 (79)
Prior basal cell carcinomas	
1–2	187 (39)
3–5	194 (40)
> 5	99 (21)

Risk of Developing an Adverse Reaction

Of the 491 patients in the placebo control group, 480 had complete information for all covariates and were included in the analysis. Of these 480 patients, 195 (41%) had at least one adverse reaction over the course of the follow-up. The baseline characteristics of the 480 patients in this analytic set did not significantly differ from those of the entire placebo control group (n = 491).

Of the nine risk factors analyzed in the multivariate logistic model, only clinical center was significantly related to the development of an adverse reaction (χ^2 21.8, 7 df, P = 0.0027). Individual covariate analysis demonstrated that patients attending clinical center 5 were 2.7 times more likely to develop an adverse reaction compared to patients attending clinical center 1 (95% CI: 1.26, 5.82; P = 0.01) while patients at clinical center 7 were 2.5 times more likely to develop an adverse reaction compared to those at clinical center 1 (95% CI: 1.22, 5.31; P = 0.01) (Table 2).

Risk for the Number of Adverse Reactions Developed over 36 Months of Follow-up

The additional constraint of a full 36 months of follow-up further reduced the number of patients in this analytic set. Of the 491 patients in the placebo control group, 441 had complete information on all covariates analyzed *and* were followed for the full 36-month intervention period. The distribution of baseline characteristics of patients in this group did not differ significantly from the group analyzed

TABLE 2. Odds ratios and 95% confidence intervals for risk of an adverse reaction by baseline risk category

Baseline covariate	Odds ratio	95% confidence interval
Age ⩾ 63 y	1.11	0.60, 2.08
Male gender	1.46	0.87, 2.45
College education or greater	1.20	0.78, 1.84
Marital status		
Single	0.35	0.09, 1.34
Widowed	0.63	0.23, 1.75
Divorced/separated	1.11	0.46, 2.68
Clinical center		
2	0.71	0.32, 1.56
3	1.05	0.53, 2.10
4	1.09	0.53, 2.25
5	2.70	1.26, 5.82
6	1.51	0.71, 3.22
7	2.55	1.22, 5.31
8	0.67	0.27, 1.67
Ever smoked	0.90	0.58, 1.38
Very fair skin	0.93	0.55, 1.57
Prior basal cell carcinomas		
3–5	0.99	0.64, 1.53
> 5	1.40	0.82, 2.40

AEP Vol. 4, No. 4
July 1994: 327–331

by logistic regression. Of these 441 patients, 179 (41%) had one or more adverse reactions over the intervention period. The number of reactions per patient ranged from one to seven (median, two).

The results of multivariate log-linear regression analysis generally paralleled the results found with logistic regression. Once again, clinical center was the only significant predictor for the number of adverse reactions that developed over the 36-month intervention period (χ^2 46.69, 7 *df*, $P < 0.000001$). On average, patients at clinical centers 5 and 7 had almost twice as many reactions as patients at clinical center 1, after adjusting for all other covariates in the model ($P = 0.0008$ for both) (Table 3). Interestingly, patients at clinical center 2 had on average 40% fewer adverse events than did patients attending clinical center 1, and this result was of borderline significance ($P = 0.0595$, 95% CI: 0.352, 1.021) (see Table 3).

DISCUSSION

The frequency and type of adverse effects elicited are strongly influenced by the study protocol and the methods for detecting and recording events, the side effects and dose of the active drug used, and the therapeutic effect achieved (1). Other investigators have observed a correlation between active treatment and placebo groups in the profile and pattern of adverse reactions (8, 20). We also observed a similarity between the intervention and placebo groups in the distribution of clinical adverse effects (15).

TABLE 3. Count ratios[a] for average number of adverse reactions developed over 36 months of intervention and associated 95% confidence intervals by baseline risk category

Baseline covariate	Count ratio	95% confidence interval
Age ≥ 63 y	1.30	0.92, 1.83
Male gender	1.18	0.89, 1.57
College education or greater	1.00	0.79, 1.27
Marital status		
Single	0.92	0.50, 1.70
Widowed	0.64	0.32, 1.26
Divorced/separated	0.88	0.52, 1.48
Clinical center		
2	0.60	0.35, 1.02
3	1.32	0.89, 1.96
4	0.87	0.56, 1.37
5	1.97	1.32, 2.93
6	1.21	0.78, 1.88
7	1.98	1.33, 2.94
8	0.76	0.43, 1.34
Ever smoked	1.09	0.86, 1.38
Very fair skin	0.83	0.63, 1.09
Prior basal cell carcinomas		
3–5	0.87	0.68, 1.11
> 5	1.02	0.76, 1.38

[a] Count ratio is defined as the ratio of the average number of adverse reactions over 36 mo of intervention for the covariate to the average number of adverse reactions over 36 mo of intervention in the reference group, adjusted for all other covariates in the model.

We were unable to corroborate the findings of others that educational level (3), age, and gender (10) can sometimes predict the development of adverse reactions. Except for clinical center, none of the baseline characteristics examined were predictive of the risk for developing an adverse reaction or for developing more adverse reactions. On the one hand, the homogeneity of our clinical trial population may have attenuated our ability to detect any potential risk factors. On the other hand, this may confirm that the placebo response is seldom consistent, constant, or predictable, depending more heavily on the personality of the user in combination with factors such as who prescribed the placebo and under what circumstances it was administered (21, 22). In a clinical trial, there are many factors that can influence the placebo effect. In addition to the overall trial environment, the increased attention shown to patients participating in a clinical trial, and the patients' expectations and belief in the efficacy as well as in the potential toxicity of the drug being tested are important components of the placebo "effect" (23–25).

Our main finding that clinical center was the strongest predictor of both the presence and the number of placebo adverse reactions is interesting in light of the intensive effort we made to standardize the process of eliciting, classifying, documenting, and managing adverse reactions in this trial. This points out the difficulty in controlling for the inherent differences in the characteristics of the patient populations and clinic personnel at the clinical centers in a multicenter trial and emphasizes the need to stratify by clinical center prior to randomization.

The potential for placebo treatment to induce adverse reactions in as much as 40% of patients should stress the need for caution in interpreting uncontrolled or isolated case report data evaluating a drug's toxicity. The importance of incorporating both a control group and a uniform system of adverse reaction detection and classification in drug evaluations cannot be overemphasized.

REFERENCES

1. Haegerstam G, Huitfeldt B, Nillson BS, et al. Placebo in clinical drug trials—A multidisciplinary review, Methods Find Exp Clin Pharmacol. 1982;4:261–278.

2. Batterman RC. Placebo and non-reactor to analgesics, Fed Proc. 1957; 16:280.

3. Beecher HK. The powerful placebo, JAMA. 1955;159:1602–1606.

4. Beecher HK. Measurement of Subjective Responses: Quantitative Effects of Drugs. New York: Oxford Univ. Press; 1959.

5. Doongaji DR, Vahia VN, Bharucha MPE. On placebo, placebo responses and placebo nonresponders. Part II: Psychopharmacological and psychophysiological factors, J Postgrad Med. 1978;24:147–157.

6. Wolf S, Pinsky RH. Effects of placebo administration and occurrence of toxic reactions, JAMA. 1954;155:339–341.

7. Wolf S. The pharmacology of placebos, Pharmacol Rev. 1959;11:689–704.

8. Pogge RC, Coats EA. The placebo as a source of side effects in normal people: Influence of gradually increasing doses, Nebr Med J. 1962;47:337–339.

9. Green DM. Pretreatment symptoms in the evaluation of drug side effects (abstract), Pharmacologist. 1963;5:234.

10. Green DM. Pre-existing conditions, placebo reactions and "side effects," Ann Intern Med. 1964;60:255–265.

11. Reidenberg MM, Lowenthal DT. Adverse non-drug reactions, N Engl J Med. 1968;279:678–679.

12. Myers MG, Cairns JA, Singer J. The consent form as a possible cause of side effects, Clin Pharmacol Ther. 1987;42:250–253.

13. Moscucci M, Byrne L, Weintraub M, Cox C. Blinding, unblinding, and the placebo effect, Clin Pharmacol Ther. 1987;41:259–265.

14. Tangrea JA, Edwards BK, Taylor PR, et al. Long-term therapy with low-dose isotretinoin for prevention of basal cell carcinoma: A multicenter clinical trial, J Natl Cancer Inst. 1992;84:328–332.

15. Tangrea JA, Adrianza ME. Helsel WE, et al. Clinical and laboratory adverse effects associated with long-term, low-dose isotretinoin: Incidence and risk factors, Cancer Epidemiol Biomarkers Prev. 1993;2:375–380.

16. Tangrea JA, Edwards BK, Hartman A, et al. Isotretinoin–Basal Cell Carcinoma Prevention Trial: Design, recruitment results and baseline characteristics of the trial participants, Controlled Clin Trials. 1990;11:433–450.

17. Tangrea JA, Adrianza ME, McAdams M. A method for the detection and management of adverse events in clinical trials, Drug Inf J. 1991;25:63–80.

18. Statistical Analysis System (SAS Version 6.07). Cary, NC: SAS Institute; 1992.

19. Fitzpatrick TB. Soleil et peu, J Med Esthet. 1975;2:33–34.

20. Cromie BW. The feet of clay of the double-blind trial, Lancet. 1963;9:994–997.

21. Kurland AA. The drug placebo–Its psychodynamic and conditional reflex action, Behav Sci. 1957;2:101–110.

22. Shapiro AK. The placebo effect in the history of medical treatment: Implications for psychiatry, Am J Psychiatry. 1959;116:298–304.

23. Rashkis HA, Smarr ER. Psychopharmacotherapeutic. A triadistic approach, Arch Neurol Psychiatry 1957;77:202–209.

24. Schindel L. Placebo und Placebo-Effekte in Klinik und Forschung, Arzneimittel Forschung. 1967;17:892–918.

25. Schindel L. The placebo dilemma, Eur J Clin Pharmacol. 1978;13:231–235.